

## **REMARKS**

As a preliminary matter, Applicants thank the Examiner for the telephonic interview held on October 27, 2006, with their attorney, Mr. Jeffrey Rosedale, Mr. Aaron Rabinowitz, and with the first-named inventor, Dr. Jason West. During the interview the art of record was clearly discussed and distinguished. In particular, it was discussed how the “Mathies Reference” clearly does not disclose microarrays. Applicants note that the Examiner states in his Interview Summary that, “Applicant described that the invention of the instant application is beneficial because it offers purification and detection of analytes on a single chip, thereby increasing the speed of the process, and decreasing contamination and degradation of analytes.” Interview Summary at 3. Applicants respectfully submit that these are not the only benefits of their invention.

### **I. Rejections under 35 U.S.C. § 103**

#### **1) Mathies in view of McNeely**

Claims 1-11, 55-64, 66, 68-77 and 111-114 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over U.S. Pat. App. No. 2004/0209354 to Mathies *et al.*, (“the Mathies application”) in view of U.S. Pat. App. No. 2004/0037739 to McNeely *et al.* (“the McNeely application”). Applicants respectfully submit that this rejection is improper because the office action does not set forth the basic requirements of a *prima facie* case of obviousness that is required by MPEP § 2143.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art and not be based on applicant's disclosure. MPEP § 2143; *In re Vaeck*, 947 F.2d 488, 20 USPQ 2d 1438 (Fed. Cir. 1991).

Applicants submit that the Office Action does not properly set forth all three of these requirements and therefore the rejection should be withdrawn. As described below, Applicants show how one of ordinary skill in the art would not be motivated to combine the Mathies and McNeely applications to arrive at their claimed invention and that one of ordinary skill in the art would not have a reasonable expectation of creating any claimed invention merely by combining the teaching of the Mathies and McNeely applications. Further, Applicants submit that the Office Action's assertions of the claimed invention's obviousness are, at least in part, impermissibly based on "common knowledge" and lack the necessary record support required under MPEP § 2144.03 for factual assertions the Examiner makes to support an obviousness-based rejection of claims.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. MPEP § 2143.01; *In re Mills*, 916 F.2d 680, 16 USPQ 2d 1430 (Fed. Cir. 1990). Claim 1 of the present invention, upon which all other claims depend, recites a microfluidic chip comprising a plurality of vias; a functionalized porous polymer monolith capable of being in fluid communication with at least one of said vias; a microarray capable of being in fluid communication with said functionalized porous polymer monolith; and an observation port through which at least one target disposed within said microarray is capable of being detected. Applicants submit that neither the Mathies nor the McNeely applications suggest the desirability of combining any of its disclosed microfluidic elements to arrive at Applicants' microfluidic chip having an observation port through which at least one target disposed within said microarray is capable of being detected.

The Office Action asserts at pages 2-3 that it "would have been obvious at the time of the claimed invention to utilize the microarray disclosed by Mathies not only for purification purposes, but also for detection purposes." Applicants submit that the Office Action's statement that Mathies discloses "microarrays" is incorrect. Moreover, Mathies' **failure** to disclose microarrays **negates** any assertion that Mathies renders the claimed invention obvious.

A **microarray** is described in the instant specification at paragraph [0035] as "a collection of probes synthesized, attached, or deposited on a substrate." In addition, the

McNeely reference describes a **microarray** at paragraph [0006] as, “multiple spots of reactant molecules on a planar substrate . . .” As distinct from microarrays, however, the Mathies application describes microfluidic devices that have fluid control structures comprising monolithic elastomer membranes associated with an integrated pneumatic manifold for the placement and actuation of a variety of fluid control structures (abstract); nowhere does Mathies describe microarrays.

As discussed in Applicants’ previous response, **FIG. 11** in the Mathies application illustrates an embodiment of a microfluidic chip comprising *inter alia* an “Immuno-affinity Capture Chamber” 1101, which is fluidically connected to a separate PCR Chamber 1103, which is fluidically connected to a **separate** Capillary Electrophoresis (“CE”) channel 1113. Accordingly, one of ordinary skill in the art understands Mathies to teach that nucleic acids are first captured and purified in the Immuno-affinity Capture Chamber (which is not a microarray), after which these nucleic acids are then fluidically transported to the PCR chamber for amplification. The resulting amplicons are fluidically transported to the CE microchannel for separation and detection; hence, the locus of detection in the CE microchannel is spatially distinct from the locus of capture and purification in the Immuno-affinity Capture Chamber. Thus, Applicants respectfully submit that the Office Action is therefore incorrect in alleging that the Mathies capture chambers, as described in paragraph [0079] of that reference, can be used for the same purposes as Applicants’ microarrays.

Likewise, whereas targets are disposed in Applicants’ microarray and **detected** through an observation port, Mathies’ capture chambers are described in paragraph [0079] of that reference as being used only **to purify** target molecules:

[0079] In other examples, each capture chamber is filled with a viscous polymeric matrix containing oligonucleotide probes to selectively bind the target molecules. In the case of DNA analysis, Sanger DNA sequencing extension products, including primers and polymerase reagents in a high salt concentration, are electrophoresed through an immunocapture chamber containing the immobilized acrylamide matrix containing the covalent oligonucleotide probe. The capture sequence is chosen so that only DNA amplification products are captured by the probe, but the primers and polymerase reagents, along with salts, pass through the device. **This is not**

**unlike the need to purify target molecules from complex, dirty mixtures that will be encountered in point of care analyses.**

Thus, nowhere does the Mathies application in paragraph [0079] teach or suggest that such bound, purified, target molecules are to be **detected** in its capture chambers in the way as Applicants' microarrays (*i.e.*, capable of capturing at least one target which is capable of being detected through Applicants' observation port). In contrast, the Mathies device uses a much different method of detection, a **capillary electrophoresis ("CE") channel**, which is **separate** from the capture chambers:

[0071] According to various embodiments, **the immunoaffinity capture chambers 703, 713, and 723 are integrated with PCR chambers but CE mechanisms remain separate**. The combination of immunocapture and nucleic acid analysis dramatically enhances the sensitivity and specificity of the individual assays.

[0072] ... In many examples, **the processed samples can then be provided for CE analysis**.

[0073] Integrated immunoaffinity capture chambers are included in a pathogen analyzer. A variety of capture mechanisms can be used, such as frits, beads, gels, monoliths, and polymers. **FIGS. 8 and 9 are diagrammatic representations showing immunocapture chambers implemented using silica frits or beads**. According to various embodiments, immunocapture chambers includes a series of silica flits fabricated by filling wafer holes with a mixture of silica power and sodium silicate binder. Upon dehydration and rinsing, the silicate condenses to silica gel and **an insoluable silica flit is formed at 801, 803, 805, and 807**.

(Mathies application, at the indicated paragraphs, emphasis supplied).

Noting the that McNeely application at paragraph [0155] "teaches that optical detection windows are incorporated into the apparatus," the Office Action asserts at page 4 that, in light of Mathies and McNeely, "it would have been obvious to utilize an optical detection port in order to monitor target/ligand reactions in the capture chamber disclosed by

Mathies.” Applicants respectfully disagree and submit that one of ordinary skill in the art would **not** be motivated by McNeely to place an observation port over the capture chambers disclosed in Mathies application because Mathies detects analytes by using capillary electrophoresis that occurs at a location **spatially separate** from the capture chambers. Hence, Applicants submit that the combination of Mathies read in light of McNeely would not teach one of ordinary skill in the art the desirability of looking elsewhere in the related art (such as to McNeely) to combine an observation port with capture chambers. For these reasons, Applicants request that this rejection for alleged obviousness be withdrawn. Any claim depending from an independent claim nonobvious under 35 U.S.C. 103 is itself nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ 2d 1596 (Fed. Cir. 1988). Accordingly, all of the remaining claims 2-114, which depend from independent claim 1, are also nonobvious for these reasons.

Even if the Examiner has set forth a *prima facie* case of obviousness (and Applicants are not conceding he has), Applicants traverse the rejection under 35 U.S.C. §103(a) because the deficiency of the Mathies application (*e.g.*, providing a plurality of vias and an observation port through which at least one target disposed within the microarray is capable of being detected) is not cured by the McNeely application.

The Office Action asserts at page 19 that the McNeely application:

“[G]ives motivation that would persuade one of ordinary skill in the art to utilize the functionalized porous polymer monolith microarray in the detection of analytes, rather than simply just in their purification. Consequently, it would have been obvious to include an observation port capable of facilitating optical detection.”

Applicants respectfully disagree. Read literally, the Office Action statement suggests that Mathies and McNeely teach the immobilization of functionalized porous polymer monoliths on a substrate on which detection of analytes trapped on the monoliths is performed by inspecting such monoliths through an observation port. However, neither Mathies nor McNeely disclose an observation port used for viewing capture chambers or functionalized porous polymer monoliths. As discussed above, Mathies does **not** disclose the use of microarrays, and McNeely does not disclose the use of microarrays in purification. Further, Applicants disclose at paragraph [0060] the use of functionalized porous polymer monoliths

to purify and label target molecules and at paragraph [0050] disclose the use of microarrays for subsequent detection of purified and labeled target molecules at a location spatially separate from that of the functionalized porous polymer monoliths. Hence, the Examiner's assertion that it would be obvious to include an observation port to view functionalized porous polymer monoliths does not directly relate to Mathies, McNeely, or the claimed invention. Accordingly, Applicants submit the Examiner's above-quoted statement is not relevant to the obviousness analysis of the claimed invention.

Next, the Office Action asserts at pages 4 and 19 in support of its rejection of Applicants' claims that it would be obvious to combine Mathies with McNeely on the ground that:

"It is *believed* that using microarrays for purification and using microarrays for detection are exceedingly similar acts. Both require selective binding of immobilized probes to analytes in a sample solution. Detection simply requires an additional step usually performed by an optical system. The selective binding of analytes to the microarray is identical in purification and detection procedures and therefore does not require any differences in the composition of the microarray probes." (emphasis supplied)

Applicants respectfully submit that this statement is not relevant to the claimed invention because it is factually incorrect. In addition, Applicants submit that the statement is apparently based, at least in part, on the Examiner's personal "common knowledge," which is improper in the context of an obviousness rejection without further explanation.

Applicants respectfully disagree with the Examiner's assertion that purification and detection are such "exceedingly similar acts" that one must obviously follow from the other. For example, as set forth in the example at paragraph [0094] of Applicants' specification, target molecules are purified and labeled at the polymer monolith and subsequently released from the monolith and transported to the microarray where the labeled target molecules hybridize with probes spotted on the microarray for subsequent detection. Thus, purification and detection **are separated by the intermediate steps of labeling, release, transport, and hybridization** to probes. Accordingly, Applicants respectfully submit that because detection is distinct from purification in that detection requires **more** than the single additional step of optical inspection of immobilized molecules, the Examiner is mistaken in asserting that the

act of detection is obvious in light of the act of purification. Accordingly, because the acts of purification and detection are separated by several intermediate steps, Applicants assert it is not obvious to utilize purification techniques in detection and that the claimed invention is therefore not obvious in view of the combination of the Mathies and McNeely references.

Furthermore, Applicants respectfully submit that the Examiner's assertion that the similarity between purification and detection is based simply on a belief is a statement that relies on the Examiner's "common knowledge," and is not, as is required in an office action, properly supported by reference to the art. See MPEP § 2144.03; *In re Zurko*, 258 F.3d 1379, 59 USPQ 2d 1693 (Fed. Cir. 2001). Applicants submit that purification and detection are multistep technical processes and assert that the Examiner's stated belief that detection and purification are similar is not "capable of such instant and unquestionable demonstration so as to defy dispute." *In re Ahlert*, 424 F.2d 1088, 165 USPQ 418 (CCPA 1970). Accordingly, Applicants submit that the rejection of Applicants' claims was improper to the extent that it was based on the Examiner's unsupported statement regarding purification and detection and respectfully request the Examiner present the evidentiary basis on which he based in an Affidavit as required by 37 CFR 1.104(d)(2). See MPEP § 2144.03.

Accordingly, in light of the non-obviousness of claim 1, Applicants request that all dependent claims related to claim 1 be allowed. As set forth in *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), any claim depending from an independent claim nonobvious under 35 U.S.C. 103 is itself nonobvious. Accordingly, Applicants submit that all of the remaining claims 2-114, all of which depend from independent claim 1, are themselves nonobvious and Applicants request they be allowed.

## **II. Conclusions**

Applicants request the Examiner to:

- (1) reconsider and withdraw the rejections of the claims; and
- (2) pass claims 1-114 to allowance.

If the Examiner wishes to discuss this matter further, he is requested to contact the undersigned attorney at 215-568-3100.

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Respectfully submitted,

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